REMARKS

The Office Action and the cited and applied reference have been carefully reviewed. No claim is allowed. Claims 93-120 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

Claims 93-119 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. This rejection is respectfully traversed.

Regarding claim 94, the examiner states that when it comes to hybridization conditions, the washing temperature is absolutely critical as to the removal of nonspecific hybridization complexes, and therefore, should always be specified. Applicants do not agree with this assertion. The stringency of "hybridization" is controlled by the combination of temperature and ionic strength of the hybridization or the wash, whichever is higher in stringency. Thus, when only the hybridization conditions are specified without specifying the wash conditions, such as in the present specification, then it would be well understood by those of skill in the art (neither vague or indefinite) that it is the hybridization conditions that control the stringency and the wash conditions are less or at most only equally stringent, but not more stringent then

the hybridization conditions. Providing only the hybridization conditions is not uncommon, particularly since hybridization at high stringency may only require removal of nonspecific hybridization at lower stringency because the background is already quite low due to the high stringency hybridization conditions. Accordingly, the wash temperature is not absolutely critical; rather, the critical feature is the highest stringency that is encountered during hybridization and wash as this determines what hybrids can be formed and what hybrids would remain after hybridization and washing. Therefore, there is nothing indefinite about specifying only the hybridization conditions and not the wash conditions, as what is intended would be well appreciated by those of skill in the art.

The remaining indefiniteness issues are obviated by the amendments to the claims.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 93, 94, 96, 118 and dependent claims 95 and 98-117 remain rejected under 35 U.S.C. §112, first paragraph, as the examiner holds that enablement is not commensurate in scope with the claims, for the reasons set forth in the previous Office Actions, paper no. 22 at page 4 and paper no. 24 at page 3.

The examiner states that the issue is not whether a skilled artisan knows how to obtain "variants of SEQ ID NO:2", and a monoclonal antibodies thereto, and how to use such SEQ ID NO:2 specific antibodies; rather, the issue is that the claims encompass antibodies that bind to epitopes of the variants, which are not found in the particularly disclosed sequence, SEQ ID NO:2, and there is no written description of those epitopes, and therefore the structural properties and use of the corresponding antibodies are not predictable.

Applicants respectfully disagree. Monoclonal antibodies which recognize epitopes of SEQ ID NO:2 and which are encompassed by claim 93 are readily obtainable for a skilled artisan without undue experimentation based on the disclosure of the present specification, i.e., IGIF/IL-18 having an amino acid sequence of SEQ ID NO:2, the disclosure on pages 15 to 19 and Example 3 at pages 42 to 48, and the state of the art (such as the disclosure in U.S. Patent No. 5,304,496, submitted with the amendment filed November 30, 2001). It is not necessary to have either concrete information about the antibodies or the amino acid sequence of those antibodies in order to obtain them. The disclosure of the present specification and the state of the art would be enough for a skilled artisan to obtain those antibodies.

Furthermore, applicants believe that structural properties would not be necessary to practice the presently claimed invention, because the structural properties are inherent to the monoclonal antibodies and therefore it is believed that the absence of the disclosure of the structural properties would have no effect either for preparation of the monoclonal antibodies or in the monoclonal antibodies *per se*.

The examiner states that "use of the corresponding antibodies are not predictable". In response, the examiner's attention is invited to the disclosure from the first paragraph at page 19 to the first paragraph at page 21 of the specification, where use of the antibodies are disclosed, including use in purification of the IFN-γ inducing protein.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 93-96 and 98-118 remain rejected under 35 U.S.C. §112, first paragraph, as lacking adequate written description for variants of SEQ ID NO:2, for the reasons set forth in the previous Office Actions, paper no. 22 at page 5, and paper no. 24 at pages 4-5. The examiner states that applicants' argument that the present invention is a pioneer invention is not persuasive because IGIF or IL-18 is not a first invention with regard to a IFN-gamma inducing substance. This rejection is respectfully traversed.

Applicants are not asserting that the present invention is a pioneer invention with regard to a substance capable of inducing IFN-gamma, but asserts that the present invention is a pioneer invention with regard to the eighteenth interleukin (i.e., IGIF/IL-18), which was isolated for the first time by applicants. It is therefore quite natural that a monoclonal antibody which specifically recognizes such IGIF/IL-18 is a new substance. Applicants believe that whether or not the present invention is a pioneer invention should not be judged from IFN-gamma inducing capability alone; otherwise, various substances known to have IFN-gamma inducing capability, such as 12-O-tetradecanoylphorbol-13-acetate (TPA: promoting agent of carcinogenesis), IL-12, and the present IGIF/IL-18 would all be categorized in the same category. In fact, it is difficult to consider these substances as belonging to the same category because of the numerous differences in physico-chemical properties, such as whether they are proteinous substances and whether they have sugar portions, as well as in their physiological activities and in the mechanism of their function, even though they have IFN-gamma inducing capability in common.

It should be emphasized that the present IGIF/IL-18 was nominated "IL-18" because it is merely the eighteenth interleukin identified. The presently claimed invention is

directed to a monoclonal antibody which specifically recognizes this "IL-18". Therefore, it is clear that the present invention is a pioneer invention. The presently claimed monoclonal antibody is a new antibody which specifically recognizes IL-18 and has industrial utility.

Nakamura does not make obvious the presently claimed invention. Accordingly, reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 93-119 remain rejected under 35 U.S.C. §103(a) as being unpatentable over Nakamura et al., Infect. Immun. 61:64-70 (1993), for the reasons set forth in the previous Office Actions, paper no. 22 at pages 6-8 and paper no. 24 at pages 5-6. This rejection is respectfully traversed.

The examiner states that applicants' argument is not persuasive because Nakamura's factor of 75 kDa is a mixture of IGIF and other substances as demonstrated by Okamura that the molecular mass of 75 kDa IGIF was reduced to 19 kDa on 0.1% SDS-PAGE in the presence of DTT, and the N-terminal amino acid sequence is the same as that of IGIF from the liver, and that "thus IGIF in the serum sample was proved to be *the same* IGIF as that found in the liver exact" (the abstract, and page 3969, the second paragraph of the left column). The examiner takes the position that even if the factor of Nakamura were a

mixture of IGIF and other substances, the 19 kDa IGIF is at least a significant component thereof. As such, the examiner asserts that a significant number of the antibodies within the genus conceded to be obvious in view thereof would have recognized epitopes on the 19 kDa component, and such antibodies are obvious over the present claims regardless of whether the IGIF of 18-19 kDa is separated.

With due respect to the examiner, applicants believe that the examiner is using hindsight reconstruction because one of ordinary skill in the art could not have expected to obtain a monoclonal antibody specific to IGIF/IL-18 from reading Nakamura's disclosure, without the teaching of the present specification.

Even if the mixture of Nakamura contains the 19 kDa IGIF recited in the presently claimed invention, Nakamura is silent about whether a monoclonal antibody of the presently claimed invention can be produced using the mixture. Furthermore, Nakamura provides no teaching about how to obtain a monoclonal antibody of the presently claimed invention from the mixture of various antibodies obtained by using the 75 kDa factor. It is therefore believed that it would have been quite difficult to isolate a monoclonal antibody of the claimed invention from the mixture of various kinds of antibodies obtained by using the 75 kDa factor.

Even if the 75 kDa factor of Nakamura is a mixture of 19 kDa IGIF recited in the present claims and other substances, the antibodies obtained by using said mixture is considered to be a mixture that contains other antibodies different from a monoclonal antibody of the present invention. It is therefore believed that the presently claimed invention is not obvious over the disclosure of Nakamura.

At page 7 of the response, the examiner indicates that applicants argue that Nakamura teaches that treatment with 2-mercaptoethanol (2-ME) resulted in augmented ability to induce IFN-γ, and that the IGIF protein recited in the presently claimed invention is clearly distinguished from the factor of Nakamura in IFN-γ inducing activity after SDS-PAGE, and is therefore unobvious over Nakamura. This argument is not deemed persuasive by the examiner because, while the examiner acknowledges Nakamura's teaching regard to 2-ME treatment, the present specification is not considered by the examiner to teach that the protein used in the assays for biological activity is eluted from SDS-PAGE. At page 23, Example 2-1, the examiner states that the specification merely discloses that the purified protein was electrophoresed in a SDS-PAGE to mainly show a single protein band with an IFN-γ inducing activity, which does not indicate that the protein after SDS-PAGE has the activity. The examiner further states

that, as shown in the functional assays in Example 2-4, "a present purified protein" is used in the assays. In view of Example 1, which is directed to "preparation of purified protein", "a present purified protein" using the functional assays demonstrated in Example 2-4 is purified using the procedure in Example 1, not from SDS-PAGE, it is asserted by the examiner that the "difference" between Nakamura's factor and the protein of the present invention in IFN-γ inducing activity of the protein after treatment on SDS-PAGE is not credible, and cannot be used to support the assertion that the two proteins are distinct.

The examiner's attention is invited to the disclosure at page 45, line 3 from the bottom to page 46, line 2 of the specification, which reads:

> The analysis of the purified protein on sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) under non-reducing conditions revealed that it … had an activity of inducing IFN-gamma…

As evident from the recitation, the protein with IFN-γ inducing activity recited in the present claims retains IFN-gamma inducing activity even after the treatment on SDS-PAGE. With regard to the activity measuring method of a protein band detected on SDS-PAGE, it is common knowledge in the art that the method is conducted through the following steps;

a) after treatment on SDS-PAGE, the gel is immersed in a solution of Coomassie brilliant blue to color proteins in the gel so as to make visible bands of proteins;

b) cut out the colored band on the gel;

c) extract the protein from the gel band using an appropriate buffer; and

d) measure the activity of the extracted protein by an appropriate method.

When the activity is measured, it is then concluded that the protein did not lose its activity on SDS-PAGE. If the examiner deems it necessary that the above be shown in declaration form, then the examiner is requested to advise applicants in the next Office Action.

It is further disclosed in Example 2-1 at page 23, referred to by the examiner, that the molecular weight of the protein recited in the present claims was measured by SDS-PAGE, and that the protein recited in the present claims was detected as a single band with IFN-γ inducing activity at the position corresponding to a molecular weight of 19,000±5,000 on SDS-PAGE.

By contrast, Nakamura teaches that the 75 kDa factor loses its activity after treatment on SDS-PAGE (page 68, middle of right column) and it is believed that the 75 kDa factor of Nakamura is a different substance from the protein

recited in the present claims and therefore cannot make obvious the presently claimed invention.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

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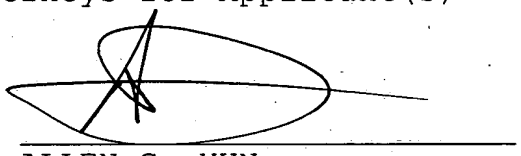
By 
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